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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/846,637	04/30/2001	Michael C. Jensen	24751-2502	4845
34055	7590	10/19/2005	EXAMINER	
PERKINS COIE LLP POST OFFICE BOX 1208 SEATTLE, WA 98111-1208			PAK, YONG D	
			ART UNIT	PAPER NUMBER
			1652	

DATE MAILED: 10/19/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application No.</b> 09/846,637	<b>Applicant(s)</b> JENSEN, MICHAEL C.	
	<b>Examiner</b> Yong D. Pak	<b>Art Unit</b> 1652	

**-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 28 July 2005.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 73, 74, 142, 143, 219, 220, 234, 235, 248 and 249 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 73, 74, 142, 143, 219, 220, 234, 235, 248 and 249 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
a) ☐ All    b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)  | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                                   | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

## **DETAILED ACTION**

### ***Continued Examination Under 37 CFR 1.114***

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on July 28, 2005 has been entered.

Claims 73-74, 142-143, 219-220, 234-235 and 248-249 are pending.

### ***Response to Arguments***

Applicant's amendment and arguments filed on July 28, 2005, have been fully considered and are deemed to be persuasive to overcome the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. Specifically, Applicant's arguments with respect to the rejection of claims 73-74, 142-143, 219-220, 234-235 and 248-249 under 35 U.S.C. 103(a) have been considered but are moot in view of the new ground of rejection under 35 U.S.C. 103(a).

### ***Claim Objections***

Claims 219-220, 234-235 and 248-249 are objected to because of the following informalities: Claims 219-220, 234-235 and 248-249 are objected for improper

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grammar. The claim recites the word "to" instead of "of" in line 6 or 7 which alters the overall meaning. Appropriate correction is required.

***Claim Rejections - 35 USC § 101***

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 73-74, 142-143, 219-220, 234-235 and 248-249 are rejected under 35 U.S.C. 101 because the claimed invention is directed to a non-statutory subject matter.

Claims 73-74, 142-143, 219-220, 234-235 and 248-249, as written, are directed to non-statutory subject matter. Claims 73-74, 142-143, 219-220, 234-235 and 248-249 are broadly drawn to a method altering the genetic makeup of a cell which could still be attached to a human being. Such methods of altering the genetic make-up of a human being are considered non-statutory subject matter. Examiner urges applicants to make appropriate amendment such that the claims do not read on a human being. Examiner suggests the use of the phrase "isolated first eukaryotic cell relative to an isolated second eukaryotic cell", for example in claim 73.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

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Claims 73-74, 219-220, 234-235 and 248-249 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 73-74, 219-220, 234-235 and 248-249 recite the phrase "selective proliferation, viability or proliferation and viability". The metes and bounds of the phrase in the context of the claims are not clear. It is not clear to the Examiner how a method can provide for selective (1) proliferation and (2) viability or proliferation and (3) viability. Examiner requests clarification of the above phrase.

Claims 73-74, 142-143, 219-220, 234-235 and 248-249 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 73-74, 142-143, 219-220, 234-235 and 248-249 recite the term "viability". The metes and bounds of the term in the context of the above claims is not clear to the Examiner. It is not clear to the Examiner as to how one skilled in the art can conclude that a cell exhibits greater "viability" than another set of cells. A perusal of the specification did not provide a clear definition for the above phrase. Without a clear definition in terms of numerical value, those skilled in the art would be unable to conclude a cell as exhibiting greater "viability". A cell is either "viable" or "non-viable", i.e. dead. A cell cannot have "greater viability".

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Claims 73-74, 142-143, 219-220, 234-235 and 248-249 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 73-74, 142-143, 219-220, 234-235 and 248-249 recite the phrase "greater proliferation". The metes and bounds of the phrase in the context of the above claims is not clear to the Examiner. It is not clear to the Examiner as to how one skilled in the art can conclude that a cell exhibits "greater proliferation" than another set of cells. A perusal of the specification did not provide a clear definition for the above phrase. Without a clear definition in terms of numerical value, those skilled in the art would be unable to conclude a cell as exhibiting "greater proliferation".

Claims 73-74, 142-143, 219-220, 234-235 and 248-249 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 73-74, 142-143, 219-220, 234-235 and 248-249 recite the phrase "introducing a nucleic acid". The metes and bounds of the phrase in the context of the claims are not clear. It is not clear to the Examiner whether applicants mean that the cell is transformed or translated with said nucleic acid into the cell. If that is so, amendment the claim accordingly would overcome this rejection. Examiner requests clarification of the above phrase.

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Claims 73-74 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 73-74 recite the phrase "exposing..cells.. to conditions". The metes and bounds of the phrase in the context of the claims are not clear. It is not clear to the Examiner what are those conditions in which an unaltered human IMPDH is inhibited but to which the altered human IMPDH is resistant to. A perusal of the specification did not provide a clear definition for the above phrase. Examiner requests clarification of the above phrase.

Claims 73, 142, 219, 234 and 248 and claims 74, 143, 220, 235 and 249 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 73, 142, 219, 234 and 248 recite the phrase "set forth in". The metes and bounds of the phrase in the context of the claims are not clear. It is not clear to the Examiner if the recited amino acid sequence has the amino acid sequence of SEQ ID NO:4 or is a representative member of a genus. Examiner suggests amending the phrase as "the amino acid sequence of SEQ ID NO:4" to clearly indicate that the nucleic acid used in the method encodes the amino acid sequence of SEQ ID NO:4.

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Claims 73, 142, 219, 234 and 248 and claims 74, 143, 220, 235 and 249 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 73, 142, 219, 234 and 248 recite the phrase "substantially identical or similar to". The metes and bounds of the phrase in the context of the above claims are not clear to the Examiner. It is not clear to the Examiner what is considered as "substantially identical or similar to" by the applicants. A perusal of the specification did not provide a clear definition for the above phrase. Without a clear definition, those skilled in the art would be unable to conclude if a eukaryotic cell is "substantially identical or similar to" another eukaryotic cell without knowing the metes and bounds of the phrase.

Claims 73-74, 142-143, 219-220, 234-235 and 248-249 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 73-74, 142-143, 219-220, 234-235 and 248-249 recite the phrases "cell...contain" and/or "SEQ ID NO:...containing". The metes and bounds of the phrase in the context of the claims are not clear. It is not clear to the Examiner how a cell or SEQ ID NO "contains" a polynucleotide or a residue. Examiner suggests the use of the term "comprises" in place of "containing".

Claims 142-143 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 142-143 recite the phrase "selective advantage for proliferation". The metes and bounds of the phrase in the context of the above claims is not clear to the Examiner. A perusal of the specification did not provide a clear definition for the above phrase. It is not clear to the Examiner as to how one skilled in the art can conclude as having cells that have a "selective advantage for proliferation". Examiner requests clarification of the above phrase.

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 73-74, 142-143, 219-220, 234-235 and 248-249 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mortensen et al., Farazi et al., Lightfoot et al., Licht et al. and Goldstein et al.

Claims 73-74, 142-143, 219-220, 234-235 and 248-249 are drawn to a method of providing for selective proliferation, viability or proliferation and viability of human cells

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comprising polynucleotide encoding a mutant human IMPDH relative to human cells comprising a polynucleotide encoding an unaltered human IMPDH, wherein human cells expressing mutant IMPDH is resistant to IMPDH inhibitors.

Mortensen et al. (form PTO-892) discloses a method of providing for selective proliferation and /or viability of human cells comprising transformation of cells with a polynucleotide encoding a mutant enzyme relative to human cells comprising a polynucleotide encoding an unaltered human enzyme, wherein human cells expressing said mutant enzyme exhibits greater proliferation or viability due to resistance to the inhibitor of the wildtype enzyme (page 9.5.7). Mortensen et al. teaches that a selectable marker (mutant enzymes having resistance to an inhibitor of the unaltered enzyme and increasing proliferation of cells expressing said enzyme) can be used as an alternative to antibiotic-resistance marker in providing and selecting stable transfectants (9.5.1 and 9.5.13).

The difference between the reference of Mortensen et al. and the instant invention is that the reference of Mortensen et al. does not use a mutant human IMPDH as a selectable marker.

Farazi et al. (cited on previous form PTO-892) teach mutants of human IMPDH type II that are resistant to IMPDH inhibitors, which are used in chemotherapy (abstract and page 961). IMPDH is necessary for purine biosynthesis in growing cells MPA (page 961). Wildtype human IMPDH II and DNA encoding the enzyme is well known in the art (Collart et al. – form PTO-1449). Wildtype IMPDH and the mutant IMPDH of the instant invention, SEQ ID NO:4, is different at residues 190, 191, 333 and 351.

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However, Farazi et al. teaches that the wildtype sequenced by Collart et al. was incorrect, and that wild type human IMPDH II naturally has an alanine at residue 190 and Glycine at residue 191 (page 962, third full paragraph and see Sequence Alignment- form PTO-892 and comments for residues 190-191 on page 3 of Sequence Alignment). Therefore, the only difference between the mutant of the instant invention and wild type IMPDH II is at residues 333 and 351.

Lightfoot et al. (form PTO-1449) discloses a polynucleotide encoding a mutant mouse IMPDH having resistance to an IMPDH inhibitor (abstract). The mutant IMPDH of Lightfoot et al. has two point mutations, Thr-333-Ile and Ser-351-Tyr (abstract). Human wild type IMPDH type II also has a Thr at residue 333 and Ser at residue 351. Since the two mammalian enzymes are highly homologous, one of ordinary skill in the art would have been led to also mutagenize Thr-333 and Ser-351 of human IMPDH in order to make a mutant IMPDH that is resistant to IMPDH inhibitors.

Mutant human IMPDH gene is a chemoresistant gene because it is resistant to IMPDH inhibitors. Licht et al. (form-1449) discloses that chemoresistant genes are useful for gene therapy in cancer patients undergoing chemotherapy by protecting organs from adverse effects caused by the toxicity of chemotherapy (page 104). Goldstein et al. (form PTO-892) discloses that patients undergoing therapy with IMPDH inhibitors suffer from toxicity and/or susceptibility to metabolic inactivation (abstract). To remedy this toxicity and susceptibility to metabolic inactivation in patients, one having ordinary skill in the art would have recognized the benefit of increasing proliferation of cells expressing mutant IMPDH resistant to IMPDH inhibitors.

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Therefore, combining the teachings of the above references, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to practice the method of Mortensen et al. using other selectable markers, such as a mutant human IMPDH having Thr-333-Ile and Ser-351-Tyr mutations. One of ordinary skill in the art would have been motivated to combine the references in order to use mutant IMPDH as a selectable marker to provide cells that have greater proliferation than cells expressing wildtype IMPDH due to stably transfection of the cells with mutant IMPDH genes resistant to IMPDH inhibitors. One having ordinary skill in the art would have been motivated to increase proliferation of cells expressing mutant IMPDH resistant to IMPDH inhibitors to combat toxicity and/or susceptibility to metabolic inactivation suffered by cancer patients undergoing therapy with IMPDH inhibitors. One of ordinary skill in the art would have had a reasonable expectation of success since Mortensen et al. teaches a method of selecting cells that exhibit greater proliferation than cells not expressing wildtype enzyme and Farazi et al. and Lightfoot et al. teach a mutant human IMPDH resistant to IMPDH inhibitors. One of ordinary skill in the art would have had a reasonable expectation of success since Licht et al. teaches use of chemoresistant genes in gene therapy of patients undergoing cancer treatment to lower toxicity of chemotherapy and Goldstein et al. teaches patients undergoing cancer treatment with IMPDH inhibitors suffer from toxicity and susceptibility to metabolic inactivation.

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Therefore, Mortensen et al., Farazi et al., Lightfoot et al., Licht et al. and Goldstein et al. render claims 73-74, 142-143, 219-220, 234-235 and 248-249 *prima facie* obvious to those skilled in the art.

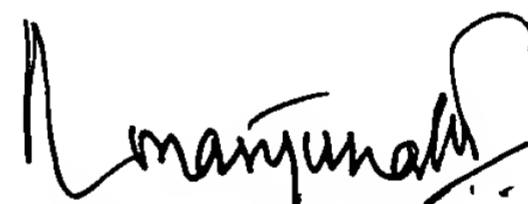
None of the claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yong Pak whose telephone number is 571-272-0935. The examiner can normally be reached 6:30 A.M. to 5:00 P.M. Monday through Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on 571-272-0928. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

Yong D. Pak  
Patent Examiner



Manjunath Rao  
Primary Patent Examiner 1652